REMARKS

Claims 1-11, 16-35, and 37-43 will remain in the application for further prosecution. Claims 1, 8, 9, 18, 19, 21, 27, and 28 have been amended to further distinguish the present invention from the cited references, which are discussed below. Claims 12-15 have been canceled.

Rejections Under 35 U.S.C. 112

Claims 6-20 have been rejected under the second paragraph of 35 U.S.C. 112, particularly with respect to the term "predetermined volume".

The Applicants' method requires that it is carried out within a device having defined physical parameters, as was previously pointed out. The term "predetermined volume" has been introduced to confirm that the Applicants' device inherently is operated in a batch manner. Fixed volumes of liquid contained in wells are transferred to chambers for mixing, the chambers being larger than the combined volume of the wells.

The Examiner appears to interpret the method claims as including the use of the microfluidic device for continuous mixing of liquids, as in the Koop device. He objects that "the issue of discrete batch mode has not been claimed" (page 8) and suggests that this applies to both the method and apparatus claims. It should be clear from the specification that the microfluidic devices of the invention inherently operate in a batch mode and the method claims are consistent. Note the discussion of the applications of the microfluidic device and the examples. Typically, a fixed (predetermined) volume of a liquid sample is added to a sample well, from which it is transferred through capillaries into a chamber in which it is mixed with reagents. Reactions

occur which are detected and correlated with the amount of an analyte in the sample. Thus, these are inherently batch operations.

Claim 1 introduces the term "predetermined volume". "Volume" refers to a fixed three dimensional space as used in Claim 1. Thus, the volume is predetermined in that it is known, as in a sample well or mixing chamber having a fixed volume. In the case of microfluidic devices the fixed volume may be 0.1 to 50 µl (paragraph 0044 or page 15, line 25). Therefore, when a first or second well contains a "predetermined volume" it means that the wells have a fixed volume, determined by the use for which the device was designed. That is, for "predetermined volume" one could substitute "volume x, where it is determined by the volume of the reagent or sample to be tested". When these predetermined volumes are combined and mixed in subsequent chambers, their combined volumes are defined with respect to the predetermined volumes of the wells supplying the chambers. Accordingly, in claim 6 the first chamber has a volume at least about twice that of the combined predetermined liquid volumes. In claims 8 and 9 the volume of the first chamber, which has at least twice the volume of the combined volumes, has a depth which is at least twice as high as the liquid in the chamber. In claims 10 and 11 at least 100 µm is provided above the liquid level. Given a defined (predetermined) volume of the sample and reagent liquids, it is possible to determine the size and dimensions of the mixing chambers.

Claims 25-28, and 29-30 also have been rejected under 35 U.S.C. 112, second paragraph, as indefinite. Again, the Examiner questions the term "predetermined volume". Claim 21 has been amended to define the volume of the chambers with regard to the liquid well volumes. It

should now be clear that the volume of the chambers can be determined since they are related to the volume of the liquids to be mixed.

Rejections Under 35 U.S.C. 102

Claims 1, 2-4, 20, 21-22 and 24 have been rejected under 35 U.S.C. 102(e) as anticipated by Koop et al ("Koop") U.S. 6,457,854. The Applicants do not agree that Koop anticipates these claims, since Koop discloses a very different device and method. Koop contains no first and second chambers, connected through one or more separated capillary passageways. Instead, Koop uses two passageways that intersect many times to mix two liquids.

The Koop device evidently is intended to operate with continuous introduction of two liquids and with the device full of liquids, as was shown previously.

In contrast with the Koop device, it should be evident that the Applicant's device inherently operates in a batch manner without being completely filled. It should be obvious from Figures 1a and 2a that fixed liquid volumes determined by wells 10 and 14 are dispensed from these wells by overcoming stops 12 and 16 and directed into chamber 18 to create a degree of mixing. The mixing process is completed by forcing the combined liquids into a second chamber through one or more capillary passageways. Advantageously, the chambers are larger than the amount of liquids being mixed. That is, the device is not filled. Furthermore, the Applicant's device is particularly useful as an analytical device, which inherently receives a fixed volume of a liquid sample and brings it into contact with a second liquid e.g. a reagent, a diluent, a conditioning agent and the like. Thus, it should be evident that the Applicant's device is, not only physically differs from Koop's, but operates differently. It cannot be seen how the

Koop device could be operated in a batch manner, as the Applicants does (note the discussion at "Microfluidics Analytical Devices".

The Examiner contends that "a discrete batch mode has not been claimed in the method step nor such feature is supported in the apparatus claims." The Applicants disagree, but have further amended the claims to distinguish the Koop reference. It should be clear that the Applicants' method and device are intended to combine fixed volumes of liquids, such as a sample liquid with a conditioning agent. Thus, the Applicants' claims must refer to a batch procedure and not to a continuous flow of liquids, as in the Koop device. Note that in a batch process it is possible to introduce two liquids into a chamber at different times and still obtain mixing.

Koop has been shown above to have intended to operate his mixing device with the continuous introduction of two liquids and with the device full of liquids. The structure shown in Koop could not be used in a batch manner, since there are no inlet wells to hold defined volume of the liquids to be mixed. Furthermore, Koop lacks chambers that receive the combined liquids. Note that he says that there is "a substantially equal passage cross-section in all areas of the passage." (column 2, lines 18-19). Therefore, the two liquids can never occupy a chamber that is larger than the volume of the liquids (as in amended claims 1 and 21). Also, Koop could not introduce two liquids at different times. Otherwise, they would not be mixed, which confirms that Koop must be understood to have intended continuous introduction of two liquids at the same time.

The Examiner now attempts to interpret Koop as having a series of mixing chambers connected by two passageways. However, as indicated in the quotation from column 2, and from

the drawings, Koop's device contains uniform size passageways throughout, and therefore it does not correspond to the Applicants' device. Consequently, Koop does not disclose the inventions as claimed.

In the following, Claim 1 will be compared with the Koop device in detail, illustrating that Koop could not anticipate the present invention. Thereafter, Claim 1 will be considered as if prior to Koop to demonstrate that Koop would not infringe the Applicants claim.

Claims	Koops – as prior art
1. A method of mixing predetermined fixed volumes of two or more liquids in a microfluidic device comprising:	• Koop teaches a mixer for gas or liquids in continuous flow and not the batch mixing inherent in the Applicant's invention. Although termed a "micromixer", Koop nowhere indicates that his passageways have capillary dimensions or move liquids by capillary forces.
(a) dispensing through capillary passageways at least a first predetermined fixed liquid volume from a first well in a microfluidic device, said first well containing said first predetermined fixed liquid volume	• Koop provides no well defining a fixed volume that is to be mixed with another fixed volume of liquid. Thus, no fixed volume is defined in Koop.
and a second predetermined fixed liquid volume from a second well, in said microfluidic device, said second well, containing said second predetermined fixed liquid volume	• Again, Koop provides no well defining a fixed volume.
into a first chamber to form a combined liquid volume, said first chamber having a volume larger than said combined liquid volume;	• Koop has no chamber in which the liquids are combined. Rather, his uniform passageways merely cross and do not form a chamber, since the liquid streams cross and continue to flow downstream. The intersection of Koop's passageways could not hold a volume larger than the sum of the two passageways. The first chamber of the invention inherently refers to a batch operation, not a continuous flow of liquids as in the Koop

(b) discharging said combined liquid volume of (a) from said first chamber into a second chamber via one capillary passageway or two or more separated capillary passageways to complete mixing of said combined liquid volume, said second chamber having a volume larger than said combined volume.

Claims

1. A method of mixing predetermined fixed volumes of two or more liquids in a microfluidic device comprising:

(a) dispensing through capillary passageways at least a first predetermined fixed liquid volume from a first well in a microfluidic device, said first well containing said first predetermined fixed liquid volume and a second predetermined fixed liquid volume from a second well, in said microfluidic device, said second well, containing said second predetermined fixed liquid volume

into a first chamber to form a combined liquid volume, said first chamber having a volume larger than said combined liquid volume

(b) discharging said combined liquid volume of (a) from said first chamber into a second chamber via one capillary passageway or two or more separated capillary passageways to complete mixing of said combined liquid volume, said second chamber having a volume larger than said combined volume.

device.

- Koop sends two liquids from one intersection to another, where they again intersect. Again, Koop's intersection is not a chamber that holds the combined liquids. The second chamber of the invention also is larger than the combined volume, inherently referring to a batch mixing operation, not to continuous flow of liquids.

Koop as potential infringer

- Koop would state that his device does not mix fixed volumes, but mixes continuous liquid or gaseous flows.

- Koop would argue that he did not have a microfluidic device, since his passageways were larger than capillaries. Further he would point out that his mixing device contains no first and second wells containing fixed volumes of liquid, but instead his device contains only uniform intersecting passageways, which are inherently suited for mixing continuous flow of fluid.

- Koop would contend that the intersection of his passageways could not be considered to be a chamber having a volume larger than the volume of his two liquids. First, there was literally no chamber and the intersection could not be larger than the sum of the two liquids.

- Koop would argue that the possible use of only one capillary to transfer combined liquids from the first chamber to the second was contrary to the clear teaching of two intersecting passageways.

Rejection Under 35 U.S.C. 103

Claims 3, 6-16, 18-19, 23, 25-35, 38, 40, and 42-43 have been rejected under 35 U.S.C. 103(a) as unpatentable (i.e. obvious) over Koop. Each of these claims depends from independent Claims 1 or 21 and should be allowable if the independent claims are allowed. The Applicants contend that Claims 1 and 21 are not anticipated by Koop and that they are not obvious. If Koop teaches forcing two liquids into intersecting sinusoidal passages, it does not follow that one skilled in the art would substitute two chambers connected by one or more separated capillary passageways, since laminar flow would be expected.

The subject matter claimed in dependent claims 3, 6-16, 18-19, 23, 25-35, 38, 40, and 42-43 does not involve optimum values reached by routine skill in the art, since the two devices are very different. Optimizing Koop, who teaches a very different mixing device, cannot be considered to produce the Applicants' device.

Claims 5, 17, 37, 39, and 41 have been rejected under 35 U.S.C. 103(a) as unpatentable over Koop in view of Nakajima et al (Nakajima). The deficiencies of Koop have already been discussed. Nakajima described an improved device to create emissions from a dispersed phase and a continuous phase, which emulsions contain microspheres. The Nakajima device employs structures that are far different from those of the Applicants' device. The Examiner relies on "obvious to one skilled in the art" to combine Nakajima with Koop. However, there is no suggestion anywhere that combining Nakajima with Koop would yield the Applicants' invention. Furthermore, neither Koop nor the present invention involve forming emulsions. Consequently, Nakajima is non-analogous art.

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The Examiner is asked to enter the proposed amendments, reconsider his rejection, and allow the amended claims. If further amendment is believed necessary, the Examiner is invited to contact the Applicants' attorney, at the telephone number provided below.

Respectfully submitted,

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Date

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